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Abstract: INTRODUCTION There is a broad variability in the accuracy levels of MRI with regard to the local staging of prostate cancer (PCa). METHODS A prospective analysis was conducted in patients with localized PCa with MRI of the prostate before radical prostatectomy. MRI and pathology findings were independently reviewed and reported based on a standardized map of the prostate with 16 regions of interest (ROIs). Diagnostic accuracy analysis of the MRI was performed using varying prostate-subpart sizes and varying cutoffs for the radiological probability for PCa presence. RESULTS Seventy four patients were included. Using varying cutoff probabilities and varying sizes of prostate-subparts resulted in a broad range of sensitivity (6-88%) and specificity (38-100%). Lower probabilities of PCa presence and larger prostate-subparts resulted in higher sensitivity but lower specificity and vice versa. Best diagnostic performance was achieved by using prostate sextants and at least moderate probabilities for PCa presence; mean sensitivity and specificity were 38% (95% CI 13-75) and 95% (95% CI 88-98). CONCLUSION The use of varying assessment parameters strongly affects the diagnostic accuracy of MRI in the local staging of PCa. Hence, precise and standardized reporting regarding these parameters is important. In our study, using at least moderate probabilities for PCa presence on MRI and prostatic sextants as ROI size was associated with best diagnostic performance.

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Influence of Varying Assessment Parameters on the Diagnostic Accuracy of Magnetic Resonance Imaging in the Local Staging of Prostate Cancer

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Key Words
Prostate cancer · Local staging · MRI · Assessment · Parameters

Abstract
Introduction: There is a broad variability in the accuracy levels of MRI with regard to the local staging of prostate cancer (PCa). ***Methods:*** A prospective analysis was conducted in patients with localized PCa with MRI of the prostate before radical prostatectomy. MRI and pathology findings were independently reviewed and reported based on a standardized map of the prostate with 16 regions of interest (ROIs). Diagnostic accuracy analysis of the MRI was performed using varying prostate-subpart sizes and varying cutoffs for the radiological probability for PCa presence. ***Results:*** Seventy four patients were included. Using varying cutoff probabilities and varying sizes of prostate-subparts resulted in a broad range of sensitivity (6–88%) and specificity (38–100%). Lower probabilities of PCa presence and larger prostate-subparts resulted in higher sensitivity but lower specificity and vice versa. Best diagnostic performance was achieved by using prostate sextants and at least moderate probabilities for PCa presence; mean sensitivity and specificity were 38% (95% CI 13–75) and 95% (95% CI 88–98). ***Conclusion:*** The use of varying assessment parameters strongly affects the diagnostic accuracy of MRI in the local staging of PCa. Hence, precise and standardized reporting regarding these parameters is important. In our study, using at least moderate probabilities for PCa presence on MRI and prostatic sextants as ROI size was associated with best diagnostic performance.

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Background

MRI is generally accepted as the most accurate and promising imaging modality for assessing the local staging of prostate cancer (PCa) [1]. It has passed through significant improvements over the last decades [2], including first and foremost a multi-parametric approach combining conventional MR with diffusion-weighted and dynamic contrast-enhanced imaging, hence, combining morphological, micro-structural and even functional information. With its high spatial resolution, it is able to detect PCa foci in difficult anatomical locations

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within the prostatic gland (i.e. the anterior zone) [3] and it even has the potential to assess the aggressiveness of PCa [4–8].

However, with MRI the reading and interpretation of the images is much more operator dependent than with other imaging modalities [9]. In the absence of generally accepted guidelines or standards for the acquisition and interpretation of prostate MR images, the quality of the image reading, its reproducibility and reduction of misinterpretation are important and mandatory prerequisites for providing high quality care to PCa patients [10].

To further improve on these crucial points, clinical studies comparing MRI findings to their gold standard, and the histological specimen, providing the essential and ultimate accuracy of the method, are important. The aim of our study was to investigate the influence of different factors on the diagnostic accuracy of MRI in the local staging of PCa as well as to define MRI performance settings for best diagnostic results.

Patients and Methods

This is a retrospective analysis of a prospectively collected data set. Patients with clinical localized PCa with preoperative MRI before undergoing radical prostatectomy have been included between January 2011 and January 2012.

All patients underwent a standardized multiparametric MRI of the prostate on a 1.5-tesla MR system (Signa EchoSpeed EXCITE HD; GE Healthcare, Milwaukee, Wis., USA) with the use of an endo-rectal coil. The standardized multiparametric image protocol consisted of unenhanced multiplanar T2-weighted and diffusion-weighted sequences. Following intravenous injection of gadoterate meglumine (Dotarem, Guerbet), dynamic contrast-enhanced MRI with fat-suppressed T1-weighted images was performed.

Radical prostatectomy was done in a robotic-assisted laparoscopic way in all cases. This study has been conducted in accordance with the rules of the local ethical committee.

Interpretation and Matching of Findings by Radiologist and Pathologist

One MRI-experienced radiologist and one experienced genitourinary pathologist interpreted their findings independently and were blinded to the other's findings, and findings were recorded along a sophisticated scheme with 16 regions of interest (ROIs) as recommended in a European consensus meeting [11]. The radiologist indicated the probability of the presence of PCa on a 4-point scale (0 = no indication for PCa presence, 1 = low probability of PCa presence, 2 = moderate probability of PCa presence, 3 = high probability of PCa presence). A specific focus was set on the presence of hematoma, indicating the probability of its presence on a 4-point scale (0 = no hematoma, 1 = small hematoma, 2 = moderate hematoma, 3 = extensive hematoma). Further, an assessment of extra-capsular growth and seminal vesicle invasion was done on a per-patient level using a 2-point scale (0 = condition not present, 1 = condition present).

The pathologist first of all performed the standardized workup of the prostatectomy specimen. He recorded the tumor extension and Gleason score by the routine protocol applied at the University Hospital of Zurich. Additionally, he recorded his findings along the 16 ROI scheme by which he indicated the presence of cancer for each ROI using a 2-point scale (0 = no tumor present, 1 = tumor present). This procedure offered a unique comparison of MR findings with final pathology.

Statistical Analysis

We assessed the influence of different cutoffs for the probability of PCa presence on MRI (low, meaning 'no indication' vs. 'at least low' probability for PCa presence on MRI; moderate, meaning 'at most low' vs. 'at least moderate' probability for PCa presence on MRI; high, meaning 'at most moderate' vs. 'at least high' probability for PCa presence on MRI) and varying ROI sizes (prostate halfs, prostate sextants and prostate 16th parts) on the diagnostic performance of the MRI. For the analysis on prostate half level, we grouped the 16 ROIs into corresponding left and right parts, for the analysis on prostate sextant level, accordingly to apex, middle and basic parts, each left and right. We used the different probabilities of PCa presence on MRI as cutoff between normal and suspicious MR findings (in detail: no vs. at least low probability; at most low vs. at least moderate probability; at most moderate vs. at least high probability of PCa presence on MRI). Since ROIs are clustered within patients, we analyzed sensitivity and specificity per patient and reported them as means with 95% bootstrap CI. Values between different situations were compared using the Wilcoxon signed ranks test.

We decided not to perform positive predictive values (PPV) and negative predictive values (NPV) analysis on prostate subpart level due to the very high prevalence of PCa positive ROIs of almost 70% in this setting, resulting in misleadingly high PPV.

Furthermore, in a clinical setting optimized for the best overall diagnostic performance of MRI (in detail: using prostate sextants and at least moderate probability of PCa presence on MRI), we calculated unadjusted and adjusted OR using clustered logistic regression. We adjusted for various variables (age, body mass index [BMI], prostate volume, preoperative prostate specific antigen [PSA], primary Gleason pattern, secondary Gleason pattern, Gleason sum score and presence of post-biopsy hematoma). Specifically, MRI findings have been used as independent variable, while pathology findings and one of age, BMI, prostate volume, preoperative PSA, presence of post-biopsy hematoma, primary and secondary Gleason pattern and Gleason score as dependent variables, as well as a robust standard error with patient ID as cluster were performed. To assess the influence of the level of probability of PCa presence on MRI on the OR, we repeated the analysis as described earlier using high probability of PCa presence on MRI.

Finally, sensitivity, specificity, PPV and NPV for extra-capsular tumor growth and seminal vesicle invasion were analyzed at a patient level, using a 2-point scale (0 = condition not present, 1 = condition present) on MRI and values are reported with Wilson 95% CI.

p values <0.05 were considered statistically significant. Statistical analyses were performed using STATA 11.2 (StataCorp, College Station, Tex., USA) and SPSS Statistics version 22 (IBM Corp., Armonk, N.Y., USA).

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Table 1. The basic characteristic of the study population (n = 74)

	Mean	Median	Range
Age, years	62	64	42–74
BMI, kg/m^2	26.5	26.2	20.1–35.5
PSA pre-operative, ng/ml*	8.7	7.2	0.75–59.9
Time from biopsy to MRI, days	66	46	6–366
Time from MRI to operation, days	30	20	1–138
Postoperative data			
Gleason score	7.2	7	6–9
Non-organ confined disease (>pT2), % (n)	23 (17 of 74)		
Seminal vesicle invasion, % (n)	8 (6 of 74)		

* One man with androgen deprivation therapy (PSA = 0.75 ng/ml).

Table 2. Impact of different cutoffs for the PCa presence on MRI and different sizes of ROIs on sensitivity and specificity

Cutoff for the probability for PCa presence on MRI	Size of ROIs		
'Normal' vs. 'suspicious'	Prostate-1/2	Prostate-1/6	Prostate-1/16
'No indication' vs. 'at least low'			
Sensitivity, % (95% CI)	88 (63–88)[6]	63 (25–88)[2]	50 (19–81)[1]
Specificity, % (95% CI)	38*	73 (55–88)[1]	86 (72–95)[1]
'At most low' vs. 'at least moderate'			
Sensitivity, % (95% CI)	50 (13–88)[7]	38 (13–75)[2]	31 (6–63)[2]
Specificity, % (95% CI)	88*	95 (88–98)[3]	98 (93–99)[3]
'At most moderate' vs. 'at least high'			
Sensitivity, % (95% CI)	25 (13–63)[8]	13 (13–38)[4]	6 (6–19)[4]
Specificity, % (95% CI)	100*	98 (90–98)[5]	98 (93–98)[5]

[1] Based on 1,000 bootstrap samples (bts), [2] 976 bts, [3] 899 bts, [4] 636 bts, [5] 668 bts, [6] 649 bts, [7] 996 bts, [8] 864 bts.
* Due to low number of patients with negative ROIs (n = 8) bootstrap not valid.

Results

A total of 74 patients were included in the study. The characteristics of these patients are summarized in table 1. The histological prevalence of PCa based on 16 ROI was 48% (573 of 1,184), based on sextants 69% (305 of 444) and based on prostate halfs 95% (140 of 148).

MRI identified PCa presence in 64% (47 of 74) using low, 34% (34 of 74) using moderate and 30% (30 of 74) using high probabilities for PCa presence on MRI as cutoff between normal and suspicious MR findings.

Both, different probabilities of PCa presence on MRI as cutoff between normal and suspicious MR findings as well as different sizes of ROIs influenced sensitivity and specificity profoundly (table 2). Specifically, sensitivity ranged from 6 to 88% and specificity from 38 to 100%, respectively. Optimizing one resulted in the deterioration of the other. Using lower probabilities of PCa presence on MRI as cutoff between normal and suspicious findings on MRI resulted in a higher sensitivity but a lower specificity, whereas using higher probabilities for PCa presence on MRI resulted in lower sensitivity but higher specificity, as we expected by definition. Applying smaller ROIs, respectively, resulted in lower sensitivity and higher specificity and vice versa. Whereas the trend in sensitivity was generally statistically significant (all p values <0.001), the trend for specificity showed only partial significance when using low probability for PCa presence on MRI as cutoff between normal and suspicious MR findings (prostate sextants compared to prostate sixteenth parts p = 0.003, prostate halfs compared to prostate sixteenth parts p = 0.046 and prostate halfs compared to prostate sextants p = 0.057).

Best diagnostic performance was achieved using prostate sextants and at least moderate probability for PCa presence on MRI (table 2). The raw sensitivity was 38%

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Table 3. Results for best diagnostic performance using prostate sextants as ROIs and at least moderate cutoff probability for PCa presence on MRI

		95% CI	p value
Sensitivity*, %	38	13–75	
Specificity*, %	95	88–98	
Unadjusted OR	4.82	2.49–9.36	<0.001
Adjusted OR**	4.58	2.34–8.98	<0.001

* Mean values taking clustering into account.
** Adjusted for Gleason pattern 1 and prostate volume.

Table 4. Results for extra-capsular tumor growth and seminal vesicle invasion on patient level

	Extra-capsular tumor growth		Seminal vesical invasion	
	%	95% CI	%	95% CI
Prevalence	23		8	
Sensitivity	12	3–34	33	10–70
Specificity	96	88–99	99	92–100
PPV	50	8–92	67	12–96
NPV	79	67–87	94	86–98

(116 of 305) and specificity 95% (132 of 139). Results for mean sensitivity and specificity as well as the ORs are summarized in table 3. An OR of 4.82 means that the odds of a ROI classified as 'at least moderate probability of PCa presence in MRI' being truly cancer affected in final pathology is almost 5 times the odds of an ROI with 'no or low probability of PCa presence in MRI'. Of the dependent variables, age, BMI, prostate volume, preoperative PSA, presence of post-biopsy hematoma, primary and secondary Gleason pattern and Gleason score, only prostate volume and the primary Gleason pattern showed to have an influence on the outcome of interest; hence, the OR adjusted for prostate volume and the predominant Gleason pattern was 4.58 (95% CI 2.34–8.98; $p < 0.001$). Using only high probabilities for PCa presence in MRI resulted in an improvement of the OR: the unadjusted OR was 6.65 (95% CI 2.18–20.3; $p = 0.001$) and adjusted for prostate volume and the predominant Gleason pattern 5.70 (95% CI 1.76–18.4; $p = 0.004$).

Finally, results for extra-capsular tumor growth and seminal vesicle invasion on patient level are summarized in table 4.

Discussion

Our study demonstrates that in the MRI of the prostate, the use of varying cutoffs for the probability for PCa presence as well as varying sizes of ROIs influenced the diagnostic accuracy of MRI both independently. Almost the full range of sensitivity and specificity can be achieved, dependent of the specific constellation of these 2 criteria used, by which sensitivity and specificity were mainly dependent on each other; that is, optimization of one lead to the deterioration of the other. Hence, a precise reporting in regard to these parameters – that is, which cutoff has been applied for the assessment – by radiologists is of utmost importance for the clinician in order to be able to interpret MRI results correctly. Our findings highlight the importance for the implementation of standardized MRI reporting guidelines. Furthermore, adherence to such reporting guidelines would help to make the results of respective studies much more comparable.

Since specificity is the main strength of MRI, assessment criteria should be optimized here for. Our findings show that using at least a moderate probability of PCa presence in MRI results in excellent specificity. However, using at least a high probability did not improve the specificity of the MRI further significantly but leads to a profound deterioration of sensitivity. Further, the use of smaller ROIs results in higher specificity while the mismatch increases with decreasing ROIs size; hence, a clinically meaningful cutoff must be defined. As a result of this study, a prostate sextant displayed a reasonable ROI size.

The observed inverse association of sensitivity and specificity when using different probabilities of PCa presence in MRI is what we would expect by definition. This means that lower probabilities result in better sensitivity and worse specificity and vice versa. However, the inverse association with varying ROI sizes needs explanation. We believe that this effect is due to different grades of mismatch. The mismatch between MRI and pathological findings will increase when using smaller ROIs and decrease when using larger ROIs, since the use of larger ROIs will result in blurring and true precision will not be achieved. Mainly, false negative findings will be reduced with consequent effects of sensitivity and specificity.

For clinical practice, our results are of importance since they help to explain the broad spectrum of diagnostic accuracy for prostate MRI found in the current literature. Recently, a systematic review and meta-anal-

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ysis of the topic has been published [12]. The study included 21 papers for analysis and the pooled sensitivity and specificity were 62% (95% CI 61–64) and 90% (95% CI 89–90). However, they found a broad variability within these results with sensitivity and specificity ranging from 29 to 94% and 39–100%, respectively. These results show the problem of inaccuracy in an impressive way and underline the importance of understanding the reasons for such variability. Whereas in most studies the size and shape of the ROIs are described in detail, the MRI assessment criteria often remain vague.

As described earlier, various previous studies showed the influence of the Gleason score (as a descriptive variable for PCa aggressiveness) on the diagnostic performance of MRI [4–8] as well as the ability of MRI to assess the aggressiveness of PCa, respectively. In contrast to these findings, our results suggest that not the Gleason sum score but rather the primary Gleason pattern seems to affect the diagnostic performance of the MRI. Hence, the aggressive pattern must have a certain volume to be identifiable by MRI. As an example, a Gleason score 8 PCa can easily be missed on MRI in case of a predominant Gleason 3 pattern and a minor Gleason 5 pattern that is only sparsely present.

Since the technical potential of MRI seems to be far away from being fully exploited, multi-parametric MRI still harbors an enormous potential to revolutionize PCa management. Especially the ability to assess aggressiveness and the ability to localize foci with high or higher aggressiveness within the prostate gland could improve the safety of gland sparing treatment approaches (like active surveillance or focal therapy) and therefore help to reduce overtreatment [13]. Besides technical improvements, the development of guidelines for a standardized image acquisition as well as guidelines for a more standardized interpretation and reporting of prostate MRI findings would be helpful to provide useful and reliable information for clinicians. To this end, further clinical studies comparing MRI findings to step-section histologic specimens are required during the coming years.

Strengths

Using a sophisticated method with corresponding ROIs to compare MR findings to histopathological specimens is clearly the main strength of our study and this allowed for a unique possibility to assess diagnostic accuracy, on patient as well as different prostate subpart levels. Furthermore, the approach allowed assessing the influence of MRI assessment criteria as well as the size of ROIs on diagnostic performance of MRI in a direct way.

Limitations

Some limiting factors must be discussed as well. First of all, the number of included patients is moderate making sub-analysis in different patient groups unreliable. Prevalence of PCa is high, even on prostate subpart levels, limiting the predictive values. Finally, we did not have a Gleason Scoring on the subpart level of the prostate (i.e. sextants as ROIs) but rather on the patient level. Hence, an adjusted analysis on the subpart level with corresponding Gleason scores within these subparts was not possible, and Gleason Scoring on patient level was taken as proxy for Gleason score on the subpart level. Hence, inaccuracy in the assessment of the influence of Gleason score and the corresponding Gleason patterns and MR findings cannot be excluded completely.

Conclusion

The use of varying assessment parameters strongly affects the diagnostic accuracy of MRI in the local staging of PCa. Hence, a precise and standardized reporting with regard to these parameters is important for the correct interpretation of MRI results. In our study, using at least moderate probabilities for PCa presence on MRI and prostatic sextants as ROI size was associated with best diagnostic performance.

Disclosure Statement

None.

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